SUPPLEMENTAL REMARKS

Based on the amendments and remarks of the response filed August 5, 2008, the discussion during the interview of January 6, 2009 and the remarks herein, reconsideration is respectfully requested.

Claims 88-92, 94-112, 135-137 and 139-144 are pending. Claims 93, 113-134 and 138 have been cancelled, and new claims 139-144 have been added.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Examiner Interview

Applicant would like to thank the Examiners Dahle, O'Hara, Gambel and Hadad for the time spent discussing this case on January 6, 2009. A number of issues were discussed during the interview.

Applicants discussed the ongoing issue of priority of variants at position 239. While agreement was not completely reached, the Examiner agreed that priority was present for 239D and 239E, and that such a statement would be put in the record. Applicants note that they have not acquiesced to the Examiner's position regarding priority for other variants at position 239.

The Presta reference and the *Ex Parte Watkins* decision were also discussed in the context of §102. Applicants reiterated their position that while non-precedential, the holding in *Ex Parte Watkins* decision is based on *In re Petering* and *Ex Parte A*, and as such, Applicants believe the recited 239 species are patentable over the teachings of Presta. The Examiner graciously agreed to consider these arguments.

The use of the Presta reference as §103 art was also discussed, particularly in the context of the patentability of a species over a genus.

Applicants discussed the introduction of the language of new claims 139-144, which the Examiner agreed to consider. Applicants also indicated their intention to keep the current language and add new claims with this new language. A subsequent communication from the Examiner during another interview on an unrelated case on January 7, 2009, indicated that the language discussed as exemplified in Claim 139 would be acceptable. Accordingly, new claims 139-144 utilize this language.

During the interview the possibility of rejoinder was discussed, and in the interests of expediting the allowance of the claims, Applicants agreed to cancel the "method of treatment" claims with the intention of filing a divisional application. Applicants reiterate that they have not dedicated or abandoned any unclaimed subject matter, particular these method of treatment claims.

Discussion of §103 in light of Presta

During the interview, Examiner Gamble discussed augmenting the Applicants' arguments in relation to the §103 rejection over the Presta reference. Applicant offers the following additional arguments.

As discussed below, Applicants maintain that the recited species are patentable over Presta. Assuming, *arguendo*[1], that Presta teaches making modifications at position 239, Applicants maintain that the specific 239 variants recited in the claims are not obvious. Furthermore, Applicants maintain that the specific 239 variants recited in the claims are not obvious over Presta whether the functional language is included in the claims or not. That is, independent claims 88, 90, 103 and 139 include the functional limitation that the variants exhibit increased binding to an FcγR receptor, while claims 89, 91, 92, 96, 97, 135, 136, 140 and 141 do not.

Species Patentable over a Genus

As stated in Takeda v. Alphapharm, 492 F.3d 1350, (Fed. Cir. 2007), the factors for evaluation of obviousness are:

[1] As discussed in the interview, Applicants do not accept that Presta legitimately teaches making modifications at position 239 to increase binding to an FcγR receptor. However, Applicants acknowledge the existence of claim 13 and thus will argue accordingly, reserving the right to argue this point in this or other cases.

> 1) "the scope and content of the prior art"; 2) the "differences between the prior art and the claims"; 3) "the level of ordinary skill in the pertinent art"; and 4) objective evidence of nonobviousness. KSR, 127 S.Ct. at 1734 (quoting Graham, 383 U.S. at 17-18, 86 S.Ct. 684).
>
> The Court went on to say:
>
> The KSR Court recognized that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." KSR, 127 S.Ct. at 1732. In such circumstances, "the fact that a combination was obvious to try might show that it was obvious under § 103." Id. That is not the case here. Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound. Thus, this case fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious if it was "obvious to try." The evidence showed that it was not obvious to try. (Emphasis added).

Applicants argue that this is very similar to the situation at hand. The Federal Circuit in *Takeda* started with a discussion of the differences between the prior art and the claims by discussing the selection of a compound as a lead compound. Following this line of reasoning, the first question is whether one of skill in the art would select S239A as a "lead compound" upon which to experiment in order to achieve better FcγR binding. Applicants submit that this is not likely, as S239A had decreased binding to four of the five tested receptors, with the fifth, FcRn, showing similar binding to wild-type[2].

The Federal Circuit went on to discuss the choice of the claimed compounds and stated:

> The district court found nothing in the prior art to suggest making the specific molecular modifications to compound b that are necessary to achieve the claimed compounds. In reaching that conclusion, the court first found that the process of modifying lead compounds was not routine at the time of the invention. page 1350

Again, Applicants argue the similarity of the present case. There is no motivation to make the specific amino acid modifications claimed in the present case, with or without

[2] Applicants further note that the lack of a standard deviation number for the binding of S239A to FcRn also brings into question whether this variant actually does have similar binding to wild type.

functional language. As shown in *Takeda*, different changes had unpredictable outcomes. Here, the Presta reference itself shows that different amino acid substitutions at the same position renders dramatically different results. For example, S267A shows increased binding to both FcγRII and FcγRIII, while S267G essentially eliminates FcγRIII binding. Another example is at position 269: E269A and E269Q both show decreased binding to FcγRIII, while E269D shows unchanged binding to FcγRIII. In addition, some amino acid modifications have no effect on binding at all, which is similarly unpredictable. For example, E318A (negatively charged amino acid replaced by small hydrophilic residue) and E318K (negatively charged amino acid replaced by positively charged amino acid residue) both show essentially no change in binding to any FcγR. There are a number of additional examples within Presta to illustrate that this reference directly teaches the unpredictability of making amino acid changes.

Accordingly, even assuming, *arguendo*, that a prima facie case was made, the Applicants submit that these rebuttal arguments, in line with the Federal Circuit and Supreme Court positions on obviousness, render the claims patentable over Presta, whether the claims include functional language or not.

The teachings of the Presta reference as a whole

As stated in M.P.E.P. §2141.03 VI.,

> A prior art reference must be considered in its entirety, i.e. as a whole, including portions that would lead away from the claimed invention. (Emphasis in original).

There are 7 references in the specification that teach that amino acid modifications at position 239 will decrease binding to FcγRs:

> Of residues 233-239, P238 and S239 have been cited as possibly being involved in binding, but these two residues have never been evaluated by substitution or deletion. See column 3, lines 14-16.
>
> In one embodiment, the polypeptide variant with altered FcγR binding activity displays reduced binding to an Fc.gamma.R and comprises an amino acid modification at any one or more of amino acid positions 238, 239, 248, 249, 252, 254, 265, 268, 269, 270, 272, 278, 289, 292, 293, 294, 295, 296, 298, 301, 303, 322, 324, 327, 329, 333, 335, 338, 340, 373, 376, 382, 388, 389, 414, 416, 419, 434, 435, 437, 438 or 439 of the

> Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. See column 5, lines 19.
>
> The polypeptide variant of interest may display reduced binding to an FcγRIII and comprise an amino acid modification at one or more of amino acid positions 238, 239, 248, 249, 252, 254, 265, 268, 269, 270, 272, 278, 289, 293, 294, 295, 296, 301, 303, 322, 327, 329, 338, 340, 373, 376, 382, 388, 389, 416, 434, 435 or 437 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat. (col 5, lines 23-30).
>
> Table 2 recites "reduced binding to both FcγRII and FcγRIII" includes 239.
>
> To generate an Fc region variant with reduced binding to the FcγR one may introduce an amino acid modification at any one or more of amino acid positions 238, 239, 248, 249, 252, 254, 265, 268, 269, 270, 272, 278, 289, 292, 293, 294, 295, 296, 298, 301, 303, 322, 324, 327, 329, 333, 335, 338, 340, 373, 376, 382, 388, 389, 414, 416, 419, 434, 435, 437, 438 or 439 of the Fc region. (See col 22, lines 55-61).
>
> Fc region variants which display reduced binding to FcγRIII include those comprising an Fc region amino acid modification at any one or more of amino acid positions 238, 239, 248, 249, 252, 254, 265, 268, 269, 270, 272, 278, 289, 293, 294, 295, 296, 301, 303, 322, 327, 329, 338, 340, 373, 376, 382, 388, 389, 416, 434, 435 or 437. (Column 23, lines 4-9).
>
> Table 6 shows S239A has reduced binding to FcγRII (both FcγRIIA and FcγRIIB) and FcγRIIIA.

The sole reference to "increased binding" with a 239 variant is in claim 13, which **was not part of the application as filed.** The claims as filed have three claims that recite 239: original claim 14 is drawn to altered binding and recites a list of positions including 239; original claim 16 is drawn to reduced binding to an FcγR and recites a list of positions including 239; and original claim 18 is drawn to reduced binding to FcγRII and recites a list of positions including 239. Notably, original claim 23 is drawn to increased binding to an FcγR and does not recite position 239. Thus, the application as filed contains no disclosure of increased binding to any FcγR using a 239 variant.

The first time the concept of increased binding to an FcγR at position 239 was introduced was the amendment dated 12/3/02, when claim 14 changed the preamble from "altered binding" to "increased binding"; the proffered reason stated by the patentee is to conform to the restriction requirement. We note that the Applicants state that "the amendments do not introduce any new matter", a statement with which we clearly take issue.

The fact that this claim was not part of the original disclosure and is the **sole** disclosure relating to increased binding of a 239 variant lessens the strength of this teaching.

Taken together, the 7 references in the specification to **decreased** binding as a result of a change at position 239, weighed against a **single** reference that was not even part of the original disclosure, renders non-obvious claims directed to increased binding at position 239.

Applicants appreciate that "patents are relevant as prior art for all they contain" (see M.P.E.P. §2123). However, in this case, the fact that the sole teaching of increased binding using variants at position 239 was added through a preamble change during prosecution and was not contested does tip the analysis towards a finding that the reference, as a whole, does not render the claimed invention obvious.

Secondary Indicia of Non-Obviousness

As outlined by the Supreme Court in *KSR*, the secondary indicia of non-obviousness is still a relevant factor for consideration in determining non-obviousness. In this case, Applicants would like to point out the commercial success of this Fc technology, including variants at position 239.

Applicants have previously demonstrated that this technology has been licensed by a number of companies, including Genentech, Centocor, MedImmune, Boehringer Ingelheim, Roche, PDL, Chugai and Human Genome Sciences.

In fact, with specific reference to position 239, the Applicants respectfully point out that MedImmune is actually utilizing some of these variants, as evidenced by U.S. Publication No. 2008/0071063, claims 13-16, with specific 239 residues recited, including 239E, 239D, 239Q, 239N, 239F, 239T, 239H and 239Y (claim 14) and 239D (claim 16); Protein Design Labs as evidenced by WO 05102387A2, pages 50 – 51, with 239D, 239E, 239N, 239Q, 239F, 239T, 239H, and 239Y specifically recited at page 50, lines13-14; and Chugai as evidenced by U.S. Publication No. 2007/0087005, claims 3 -5, 9 and 10, with specific 239 residue aspartic acid (D) recited.

CONCLUSION

In light of the above amendments and remarks, Applicants believe that this case is now in condition for allowance. Early notification is respectfully requested. Should there be any remaining issues that remain unresolved, the Examiner is encouraged to telephone the undersigned.

Please direct further questions in connection with this Application to the undersigned at (415) 442-1000.

MORGAN, LEWIS & BOCKIUS LLP

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By: /Robin Silva/
Robin M. Silva, Reg. No. 38,304

Attorney of Record for Applicants
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Customer No.: 67374
Morgan, Lewis & Bockius LLP
One Market, Spear Street Tower
San Francisco, CA 94105
Telephone: (415) 442-1000
Facsimile: (415) 442-1001